

Application Serial No. 09/438,392  
Response to Office Action dated 11 August 2003  
Reply to Office Action mailed 10 February 2003

### REMARKS

Claims 67-83 are pending. Applicants appreciate and thank the Examiner for the reconsideration and withdrawal of the previous final rejection, as well as the acknowledgment in the present Office Action that claim 76 would be allowable if rewritten in independent form.

The Patent Office has, however, imposed a new rejection under 35 U.S.C. §103(a) of claims 67-76 and 77-83 based on a new combination of art, Louvion et al. in view of Goff et al., the combination further in view of the combined teachings of Aoyama et al., Brasselman et al., Schena et al, Draper et al. and Krebbers et al. The principal basis for the Patent Office's finding of obviousness is the alleged obviousness of exchanging the GAL4 binding site with a LexA binding site, based on the alleged teaching in Goff et al. of the interchangeability of these two elements in inducible transcription systems. Applicants respectfully traverse this rejection for the reasons set forth below.

The present claims recite a vector comprising a DNA sequence encoding a transcription factor that has (1) a promoter, (2) DNA encoding a DNA binding domain of the bacterial repressor LexA, (3) DNA encoding a transactivating domain of VP16 and (4) DNA encoding the regulatory domain of an estrogen receptor (ER), arranged in this order in the 5' to 3' direction (claim 67) (the "XVE system"). Also claimed are an isolated nucleic acid comprising these elements (claim 78) and a transgenic plant or plant cell comprising the nucleic acid (claim 79). This particular selection of elements, and specific arrangement thereof, is not taught or suggested by the prior art, and further has been found to confer a distinct and unexpected advantage over the prior art.

The primary reference, Louvion et al., discloses a transcription factor having a promoter, the DNA binding domain of GAL4, the transactivating domain of VP16 and the regulatory domain of the estrogen receptor (ER). This transcription factor is hereinafter referred to as the "GVE system." This reference further discloses a transcription factor in which the transactivating domain of VP16 and the regulatory domain of ER are switched in their order within the transcription factor. This latter transcription factor is hereinafter referred to as the "GEV system." Although the primary reference discloses these two transcription factors, it discloses that the GVE system and the GEV

AUG 18 2003

RECEIVED

TECH. CENTER 1600/2900

Application Serial No. 09/438,392  
Response to Office Action dated 11 August 2003  
Reply to Office Action mailed 10 February 2003

system are not equivalent. Specifically, the Examiner's attention is directed to Table 1 on page 131 of Louvion et al. Table 1 demonstrates that the GEV system is able to induce  $\beta$ Gal activity in KY320 cells by 202 fold and to induce  $\beta$ Gal activity in GGY1::171 cells by 126 fold. In comparison, the GVE system is able to only induce  $\beta$ Gal activity by 17 fold and by 24 fold, respectively. The GVE system does not result in as tight control of transcription regulation as the GEV system. In view of this dramatic difference in activity between the transcription factors of Louvion et al., it is submitted that there would be no motivation to select the transcription factor with the lower activity and looser regulation, i.e., the GVE system, to make the Examiner's proposed substitution of LexA for Gal4.

Furthermore, it is submitted that the teachings of the Goff et al. reference are not ones from which a person of ordinary skill in the art would draw particular guidance in arriving at the present invention. For example, Goff et al. teaches a system of gene expression control completely different from that claimed herein. The Goff et al. reference teaches that a homodimeric gene activation system leads to gene repression, not gene activation, precisely the opposite effect of that which is achieved in the presently claimed invention.

Specifically, as detailed in the Amendment and Response filed on 15 May 2002, Goff et al. teaches a heterodimeric control system, where two different receptor polypeptides together activate gene transcription. See column 2, lines 55-65 and Figures 1-3. When identical receptor polypeptides are used in the Goff et al. system to form a homodimer, the result is gene repression, not activation. See column 10, lines 13-48. The present invention, directed to a homodimeric system that achieved tight control of gene activation, is at complete odds with the teachings of Goff et al. With the system of the present claims, 100-200 fold induction of transcription is routinely achieved. See Examples 12-13 of the present application. Goff et al., on the other hand, specifically states that Class 1 receptor polypeptides, such as the estrogen receptor recited in the present claims, do not function to activate gene expression. See column 1, line 60 - column 2, line 12.

Thus, it is submitted that the alleged teaching in Goff et al. of the interchangeability of the GAL4 and LexA DNA binding domains in a heterodimeric system for gene activation (or a

RECEIVED  
AUG 18 2003  
TECH CENTER 1600/2900

homodimeric system for gene repression) would not give a person of ordinary skill in the art a sufficient expectation of success in substituting the one for the other in a homodimeric gene activation system such as that described in the Louvion et al. reference, and such as that claimed herein. Thus, the necessary element of motivation to combine or modify is not present in the asserted combination of references.

The rigorous application of the motivation element "stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness." *In re Rouffet*, 47 U.S.P.Q.2d 1453, 1458 (Fed. Cir. 1998). The Federal Circuit has repeatedly emphasized the criticality of the motivation element in the obviousness analysis, stating

"[o]ur caselaw makes clear that the best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references."

*Ecolochem, Inc. v. Southern California Edison Co.*, 56 U.S.P.Q.2d 1065, 1073 (Fed. Cir. 2000). In order to prevent the use of hindsight, the Federal Circuit

"requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed."

*In re Rouffet*, 47 U.S.P.Q.2d 1453, 1457-58, *accord Ecolochem*, 56 U.S.P.Q.2d at 1076. It is submitted that the Patent Office has used impermissible hindsight in reconstructing the invention from the various elements disclosed in the several cited references, using the Applicants' own specification as a guide to select and arrange elements to arrive at the presently claimed invention.

As the Federal Circuit stated almost 20 years ago, "[c]are must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claim in suit.'" *Grain Processing Corporation v. American Maize Products*, 840 F.2d 902, 907, 5 U.S.P.Q. 2d 1788,

RECEIVED  
AUG 18 2003  
TECH CENTER 1600/2900

Application Serial No. 09/438,392  
Response to Office Action dated 11 August 2003  
Reply to Office Action mailed 10 February 2003

1792 (Fed. Cir. 1983). As established above, the prior art does not in fact contain or suggest the precise combination and arrangement of elements that is recited in the present claims, and "[t]o draw on hindsight knowledge of the patented invention, when the prior art does not contain or suggest that knowledge, is to use the invention as a template for its own reconstruction -- an illogical and inappropriate process by which to determine patentability." *Sensonics, Inc. v. Aerosonic Corp.*, 38 U.S.P.Q.2d 1551, 1554 (Fed. Cir. 1996); *see also Heidelberg Druckmaschinen AG v. Hantscho Commercial Products, Inc.*, 30 U.S.P.Q. 2d 1377, 1380 (Fed. Cir. 1993). Without the teachings of the present application before him, a person having ordinary skill in the art would have no reason to make the modifications to the prior art necessary to achieve the present invention with any reasonable expectation of success. Lacking the motivation element, rejection under §103(a) is improper.

Finally, significant unexpected results are achieved by the present invention that are not achieved with prior art systems. With the XVE system it is possible to consistently achieve 100-200 fold enhancement of gene expression. See Examples 12 and 13 of the present specification, especially page 30. In contrast, the highest level of induction achieved with Louvion et al.'s GVE system was 17-24 fold. See, Table 1, page 131 of Louvion et al. There is no suggestion in the art that the substitution of the DNA binding domain of LexA for the DNA binding domain of Gal4 would result in a transcription factor having a higher activity. In fact, the prior art (Goff et al.), as acknowledged by the Examiner, merely discloses an interchangeability of LexA and Gal4. Thus, a skilled artisan would only expect an in-kind activity of the transcription factor with the Examiner's proposed substitution in view of the teachings of the prior art. In contrast to this expectation by a skilled artisan, the present invention achieved a 100-200 fold enhancement of gene expression. This enhancement is a factor of 4.2 -11.8 times better than the GVE system of Louvion et al. These unexpected results are a clear indication of the non-obvious nature of the present invention. *See, In re Soni*, 34 U.S.P.Q.2d 1684, 1687 (Fed. Cir. 1995) ("One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of 'unexpected results,' i.e., to show that the claimed


RECEIVED  
AUG 18 2003  
TECH CENTER 160012900

Application Serial No. 09/438,392  
Response to Office Action dated 11 August 2003  
Reply to Office Action mailed 10 February 2003

invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.”)

Thus, it is submitted that not only is there no motivation in the cited prior art to arrive at the presently claimed invention, the presently claimed invention has unexpected results over the Examiner’s proposed substitution of LexA for Gal4. Therefore, it is submitted that the claims are not obvious over the cited references. Withdrawal of this rejection is requested.

In view of the above remarks, it is submitted that the present claims satisfy the requirements of the patent statutes and are patentable over the prior art. Reconsideration and early notice of allowance are requested. The Examiner is invited to telephone the undersigned in order to expedite prosecution of the present application.

RESPECTFULLY SUBMITTED,					
<i>Name and Reg. Number</i>	Jeffrey L. Ihnen, Reg. No. 28,957				
<i>Signature</i>				<i>Date</i>	11 August 2003
<i>Address</i>	Rothwell, Figg, Ernst & Manbeck Suite 800, 1425 K Street, N.W.				
<i>City</i>	Washington	<i>State</i>	D.C.	<i>Zip Code</i>	20005
<i>Country</i>	U.S.A.	<i>Telephone</i>	202-783-6040	<i>Fax</i>	202-783-6031

2312-105.response to oa

RECEIVED  
AUG 18 2003  
TECH CENTER 1600/2900